Scientific Abstract : Assessment of Retroviral-Mediated Incorporation of HSV Thymidine Kinase and Ganciclovir in HumanMalignant Gliomas

This phase I study investigates the mechanism and safety of tumor cell transduction by a retroviral vector conveying susceptibility to ganciclovir in patients with recurrent malignant gliomas. The justification for this clinical trial rests on the theoretical appeal of retroviral therapy for a tumor that is uniformly fatal, extensive pre-clinical studies that demonstrate the safety and efficacy of the HSV thymidine kinase-ganciclovir (TK-GCV) paradigm in rodent models of malignant gliomas, and exhaustive in vitro and in vivo safety testing of packaging cell lines, retroviral vectors, and the thymidine kinase-ganciclovir TK-GCV paradigm.

Patients with recurrent malignant brain tumors usually survive less than one year. Reoperation is transiently palliative; adjuvant chemotherapy is hampered by barriers to drug delivery, tumor cell heterogeneity, and a lack of specificity for tumor cells. This protocol utilizes stereotactic techniques for intratumoral implantation of a packaging cell line which produces a retroviral vector containing the HSV enzyme, thymidine kinase, that converts ganciclovir into its toxic antimetabolite. Specificity for tumor arises from 3 sources: intratumoral injection; integration and expression of the therapeutic gene exclusively in dividing cells; and restriction of vulnerability to the ganciclovir derivative to cells replicating their DNA. In the central nervous system, normal glia and nerve cells are quiescent; the dividing tumor cells are specifically vulnerable. Rodent glioma cells transfected with the HSV-TK gene have heightened sensitivity to ganciclovir whether treated in tissue culture, as a subcutaneous mass in the flanks of nude mice, or as an intracerebral tumor in rats. (Ezzeddine 1991; Takamiya 1992). In vitro transfection, by a vector released by a packaging cell line either cografted or subsequently injected into a rodent glioma, has been demonstrated; regression of gliomas following ganciclovir treatment occurs whether the tumor is subcutaneous or intracerebral. (Takamiya 1993; Culver 1992; Ram1994; Barba 1993).

The TK-GCV paradigm has proven safe in animals (Ram 1993). Normal brain tissue adjacent to transduced tumor is not affected. Gene marking and toxicity studies have shown the following: (1) Systemic spread of vector producing cells (VPC) following intracerebral injection is limited to lymphoproliferative organs (lung, spleen, liver, intestine) and ganciclovir treatment causes no pulmonary toxicity following intravenous injection of VPC. (2) Pretreatment with dexamethasone prevents the transient neurologic illness, MRI changes, and histologic injury that otherwise accompanies intracerbral injection of VPC in rats and monkeys. (3) TK-GCV treatment of normal monkey brain causes no systemic, neurologic, or MRI detectable toxicity. Histologic analysis shows gliosis and demyelination at the injection site (Ram, 1993). High dose steroids cause immunesuppression that risks infectious complications. (4) Transduction following intracerebral tumor injection in rats is limited to tumor cells and occasional tumor endothelial cells; vasculitis and destruction of normal brain tissue do not occur. (5) The first ten human patients treated with a TK-GCV protocol suffered no ill effects (Ram, 1995).

The overall objective of this Phase I trial is to evaluate the TK-GCV paradigm in recurrent malignant gliomas. This clinical protocol permits analysis of gene marking, immunologic reaction, and histopathologic toxicity following injection at three sites within the tumor. Patients who have failed standard treatment for malignant gliomas will have their tumors biopsied to confirm recurrent malignant growth. Three sites will be sampled and then injected with a single aliquot of VPC. After an interval of five days, recurrent tumor will be resected and the injection sites will be studied histopathologically. The patients will be followed clinically and radiographically for signs of toxicity. Dose of VPC will be escalated for three groups of three patients each. Stopping criteria will be strictly observed.

The specific aims are the following: (1) to assay the density, extent, and cytologic targets of transduction by and expression of the TK gene; (2) to assess the immune response to the injection of VPC and its possible contribution to tumor cell killing; (3) to evaluate the delivery of GCV to the tumor, (4) to optimize choice of injection site by correlating functional imaging characteristics, histopathology, and proliferation indices with transgene expression, immune response, and GCV delivery; and (5) to evaluate the safety of the TK-GCV paradigm in humans.